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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

ATTACHMENT TO ADVISORY ACTION

11. CONT. Applicant's arguments have been respectfully reconsidered but have not been found persuasive.

1. Status of claims. Claims 17-37 are currently pending and are currently under examination. Please, note that the claim listing provided and filed on 01-13-2009 does not amend or change the pending claims.
2. The examiner acknowledges receiving a third executed Declaration by Dr. Peter Filipcik under 37 C.F.R. § 1.132, filed on 01-13-2009, which evidence is the same as the one submitted in the third unexecuted Declaration under 37 C.F.R. § 1.132, filed on 08-14-2008. Note that the alleged evidence of the third unexecuted Declaration by Dr. Peter Filipcik of 08-14-2008 was previously considered in the Office action of 11-13-2008 to the extent that the third Declaration was not perfected yet.

Objection withdrawn in response to Applicants' arguments or amendments:

Drawings objection

In view of applicants arguments at page 5 of Remarks that objection to the Drawings and the Specification were made in error because no amendments were made to the specification or drawings on 08-14-2008, objection to the drawings has been withdrawn.

Specification objection

In view of applicants arguments at page 5 of Remarks that objection to the Drawings and the Specification were made in error because no amendments were made to the specification or drawings on 08-14-2008, objection to the Specification has been withdrawn.

Remaining objections/ rejections in response to Applicants' arguments or amendments:

Claim Objection

Claims 17-37 remain objected to because of the following informalities. Claim 17 and 37 recite, "the molecules have truncated at least 30 nucleotides downstream of the start codon and truncated at least the 30 nucleotides upstream of the stop codon of the full length tau cDNA sequence". It is confusing whether the first 30 nucleotides of the full length tau cDNA sequence downstream the start site are truncated or the truncation begins at the 30 nucleotide position downstream of the start codon. Similarly, it is ambiguous whether the truncation 30 nucleotides upstream of the stop codon of the full length tau cDNA sequence includes the 30 nucleotides upstream of the stop codon or the truncation begins at the 30 nucleotide position upstream of the stop codon. Appropriate correction is required.

Reply to applicants' arguments as they relate to objection of Claims 17-37

At page 6 of remarks, Applicants allege that the Examiner's interpretation of claim 17 appears to be related to the recitation of "has a truncation" vs. "have a truncation" , because the claim recites "the cDNA molecule has truncated", the claim recitation is not confusing. Such is not persuasive.

Claims 17 and 37 recite, "the cDNA molecule has truncated at least 30 nucleotides downstream of the start codon and truncated at least the 30 nucleotides upstream of the stop codon of the full length tau cDNA sequence". It is confusing whether the first 30 nucleotides of the full length tau cDNA sequence downstream the start site are truncated or whether the truncation begins at the 30 nucleotide position downstream of the start codon. Similarly, it is ambiguous whether the truncation 30 nucleotides upstream of the stop codon of the full length tau cDNA sequence includes the 30 nucleotides upstream of the stop codon or whether the truncation begins at the 30 nucleotide position upstream of the stop codon. As such, Applicant's arguments are not on point.

Claim Rejections - 35 USC § 112 – enablement

Please, note that the scope of enablement was previously expanded in the Office action of 11-13-2009, in view of Applicants remarks, in light of the guidance provided in the specification and knowledge available to one of ordinary skill in the art at the time of filing the present application, **in view of the third unexecuted Filipcik Declaration** and further in view of reconsideration of search under different premises.

Claims 17-37 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A transgenic rat whose genome comprises a transgene comprising a DNA construct comprising a cDNA molecule, wherein:

the cDNA molecule is truncated, wherein the truncation starts at least 30 nucleotides downstream of the start codon and wherein the truncation starts at least 30 nucleotides upstream of the stop codon of the full length tau cDNA sequence coding for 4-repeat and 3-repeat tau protein,

the cDNA molecule comprising **SEQ ID No. 9**, said cDNA operably linked to a promoter, wherein the promoter is a Thy-1 promoter,

wherein said truncated tau protein is expressed in the rat brain and neurofibrillary pathology associated with Alzheimer's disease occurs in the rat when compared to normal rats,

does not reasonably provide enablement for any non-human transgenic animal .Moreover, the instant claims do not provide sufficient enablement for any promoter (e.g., constitutive or tissue specific) other than the Thy-1 promoter for the observed phenotype of neurofibrillary pathology in rat brain.

Reply to applicant arguments as they relate to rejection of Claims 17-37 under 35 U.S.C. 112, first paragraph, scope of enablement.

At pages 6-11 of Remarks, Applicants essentially argue that the invention is enabling for the scope of the transgenic non-human animals as Applicants have provided sufficient guidance for transgenic rats that contained both 4-repeat and 3-repeat human truncated tau as evidenced by the generation of the transgenic **rat line #318 disclosed in the specification**, the transgenic **rat line # 24,** corresponding to nucleotides 277-906, SEQ ID No. 12 in Fig. 1 (See, page 2, paragraph 4 of the Filipcik Declaration filed on 09-17-2007) and **the transgenic rat line #72** comprising the construct encoding 4-repeat and 3-repeat tau protein comprising nucleotides 277-999 of tau of **SEQ ID No. 3,** which is the same construct of transgenic rat # 318 (3rd Filipcik Declaration, page 2, paragraph 5). In addition, Applicants allege that the phenotype exhibited by the three transgenic rat lines, e.g., # 24, # 72, and # 318, i.e., neurofibrillary pathology (NF) , when the DNA construct is expressed in brain cells is not dependent on the genetic background of the transgenic rat. Furthermore, Applicants refer to the publications of

Hartig et al. (European Journal of Neuroscience, Vol. 25, pp. 69-80, **2007**),
Huang et al., (Brain Research 771, 1997, 213-220),
Gotz (Brain Research Reviews 35 (2001) 266-286), and
Lewis et al., (Nat Genet. 2000 Aug; 25(4):402-5),

as further evidence that a variety of animals are capable of exhibiting NF pathology and, therefore, suitable mode for the study of NF pathology and Alzheimer's disease. Such is not persuasive.

The Examiner refers Applicants to the reasons already of record, as disclosed in the previous office action of 11-13-2009 at pages 4 to 9, particularly, to the unpredictability of the art in using transgenic animals as models for Alzheimer's disease when there is not evidence of record, at the time the invention was made, to substantiate a reasonable correlation between any non-human transgenic animals (e.g., pig, sheep, cattle, rabbit, rat, mink, monkey) exhibiting neurofibrillary pathology producing activity as a model of Alzheimer's disease, in part, due to the distinct phenotypes observed in closely related rodents such rats and mice in the expression of the same gene e.g., Amyloid Precursor Protein (APP) and, conversely, the pleitropic roles of the same gene e.g., the NF tangles associated with widely divergent neurodegenerative diseases in addition to Alzheimer's disease in terms of their pathologic mechanisms including supranuclear palsy, parkinsonism linked to chromosome 17, corticobasal degeneration, and others. Thus, the declaratory evidence is not commensurate in scope in relation to any non-human transgenic animal with the claims but only commensurate with the identified scope of enablement

At pages 12-15 of Remarks, Applicants argue the references cited in the action of 11-13-20009, specifically, Williams' reference (2000, *J. Appl. Physiol;* pp.1119-1126), Moreadith et al., (1997, J Mol Med pp. 208-216), Keefer et al., (2004, Animal Reproduction Science, pp. 5-

12) and Sigmund as they relate to the generation of any transgenic animal. Such is not persuasive.

Note that the arguments set forth by Applicants were already argued at pages 9-14 of the Action filed on 11-13-2009. In addition, the examiner directs Applicants' attention to page 12 of the Action filed on 11-13-2009 insofar as the breadth of claim 17 which does not convey germline transmission of the transgene and could also be interpreted as one cell in any non-human transgene animal that have been transformed with the claimed construct having a single cell expressing the claimed truncated tau protein. It would be unpredictable if expression of said transgene in a single cell of a transgenic non-human would result in collectable amount of the polypeptide so as to exhibit the claimed phenotype in the brain cells of the transgenic non-human animal.

In relation to the cDNA molecule coding for N- and C-terminally truncated tau molecules, Applicants contend that the scope of the cDNA molecules coding for N- and C-terminally truncated tau molecules encompassed by the claims is enable at least by the direction provide in the specification and working examples.

The examiner refers Applicants to the broadened scope of enablement as set forth in the action of 11-13-2009 and reiterated in the paragraph above, said transgenic rat genome comprises the full length of the minimal truncated tau cDNA molecule of SEQ ID No. 9, with or without any additional nucleotides at either or both ends, the truncation starting at least 30 nucleotides downstream of the start codon and wherein the truncation starts at least 30 nucleotides upstream of the stop codon of the full length tau cDNA sequence having truncated at least 30 nucleotides downstream of the start codon and truncated at least 30 nucleotides upstream

of the stop codon of the full length tau cDNA. Hence, the broadened scope of claim 17 and 37 encompass cDNA constructs coding for the N- and C-terminally truncated tau protein molecules as set forth in sequences of SEQ ID No. 1-14 as illustrated in Fig. 1

Insofar as the use of a construct lacking a promoter for functional expression of a protein at sufficient level to exhibit the claimed phenotype in the transgenic non-human animal, Applicants essentially argue that use of numerous promoters functionally linked to a gene of interests was readily available to those in the art, and as such, there is not need to recite in the claims embodiments that are well known in the art. Additionally, Applicants allege numerous promoters are known and ready available in the art to drive transgene expression in the central nervous system of various mammals including the CMV promoter, as such, it would only require routine cloning procedures to place the cDNA molecule coding for N- and C-terminally truncated tau molecules under the control of the appropriate promoter. Such is not persuasive.

The examiner refers applicants to the reasons already of record as set forth at pages 14-16 of the previous action of 11-13-2009. Since the functional linkage of a target gene to a promoter for its expression was well known in the art, Applicants have not provide sufficient guidance for how to make and use promoterless DNA constructs able to efficiently express a gene of interest. Furthermore, Applicants do not provide an enabling disclosure for the use of any promoter resulting in efficient expression of the truncated tau protein in the rat CNS to exhibit the claimed phenotype such as the CMV promoter. As the CMV promoter, for example, is active in a wide range of tissues and drives high-level constitutive expression, it will generate a transgenic non-human animal exhibiting global expression of the truncated tau gene that will necessarily result in a different transgene phenotype.

In relation to claim 37, Applicants allege that the examiner has not provided any specific reasons for rejecting this independent claim. As such applicants request withdraw the rejection of claim 37 under 35 U.S.C. 112, first paragraph, scope of enablement. Such is not persuasive.

While claim 37 has partially overcome some of the enabling issues, some issues remain in relation to the breadth of a transgenic rat having germ and somatic cells which does not convey germline transmission of the transgene and could also be interpreted as one cell in any non-human transgene animal that have been transformed with the claimed construct having a single cell expressing the claimed truncated tau protein. In addition, claim 37 broadly encompasses a genus of promoters functional in the claimed transgenic rat so as to exhibit a NF pathology in the brain. The examiner refers Applicants to the reasons already of record and the reasons set forth in the paragraphs above. Hence, the scope of the patent protection sought by the Applicant as defined by claim 37 fails to correlate with the scope of enabling disclosure set forth in the specification.

Conclusion

Claims 17-37 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Maria Leavitt/

Maria Leavitt, PhD
Examiner, Art Unit 1633